

RESPONSE TO OFFICE ACTION DATED 2 MARCH 2010

Claims 1-4, 14, 16-18, 20, 24-52 are pending in the present application. Claims 17, 37-39 and 50-51 are withdrawn from consideration.

Applicant notes that in the Preliminary Amendment (Amendment A) filed 16 October 2006, Applicant requested amendment of the title to METHODS FOR PROPHYLAXIS OR TREATMENT OF CONDITIONS ASSOCIATED WITH CORTICAL SPREADING DEPRESSION. It does not appear that the amended title has been entered by the PTO. Applicant again requests amendment of the title to provide a title more clearly aligned to the scope of the invention as set forth in the claims.

1. Rejection Under 35 U.S.C. §102(b)

Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, and 46-47 stand rejected under 35 U.S.C. §102(b) over US Patent Application No. 2002/0086828 Harris (herein "Harris '828"). This rejection is respectfully traversed.

1.1. Harris '828 Fails to Expressly or Inherently Disclose CSD: Claim 1 Is Novel

Anticipation of a claim under 35 U.S.C. §102 requires that every limitation of the claim is disclosed, expressly or inherently, in the cited document. This is not the case here.

Claim 1 recites a method for preventing or treating a condition associated with **cortical spreading depression (CSD)** in a subject, comprising administering to the subject, **in an amount effective to suppress CSD**, a compound having Formula IIb or a pharmaceutically acceptable salt thereof.

Harris '828 fails to expressly disclose the method for preventing or treating a condition associated with CSD or a method including administration of an amount effective to suppress CSD.

Harris '828 also fails to inherently disclose the method for preventing or treating a condition associated with CSD or a method including administration of an amount effective to suppress CSD. The Office Action at p. 6 asserts:

it is deemed that [a method of treating a condition associated with CSD] would be **inherent** to the method of treating headaches, migraines, chronic headaches, etc. with compound such as [harkoseride] as taught by Harris. (emphasis added)

However, CSD does not occur with all headaches, including migraines. Therefore, a method of treating a condition associated with CSD is not inherent in a method of treating a migraine. Applicant submits the following evidence to support that CSD is not inherent in migraines:

CSD is just one of many possible events that can trigger a migraine headache, *i.e.* not all migraine sufferers have CSD. For example, Iadecola states:

In 15-20% of migraine sufferers, the headache is preceded by an ‘aura’...There is increasing evidence that the aura is the result of cortical spreading depression (CSD)...

See Iadecola (Feb. 2002) Nature Medicine 8(2):110-112. This means that in most migraine sufferers (75-80%), the headache is not preceded by an aura, a possible result of CSD. Furthermore, Iadecola concludes that:

[i]n the majority of patients the headache is not preceded by an aura, and it is unclear whether the aura is an absolute requirement for the headache. Although it is possible that in most patients the aura is clinically silent, there is also experimental evidence that, in contrast to the findings of Bolay *et al.*, the aura (CSD) and the headache (meningeal inflammation) are unrelated.

Id., p. 111, col. 3, emphasis added; *see also* Bolay (Feb. 2002) Nature Medicine 8(2):136-142, at p. 136, col. 2 (“[a]lthough a link between aura and headache was suspected, the cause for the pain remains unknown”). In other words, Iadecola recognizes that “aura (CSD)” is not necessarily present in all headaches – and may not even be related. *See also* Ebersberger, *et al.* (2001) Ann Neurol, 49:7-13, p. 11, col. 2 (“collectively, these results do not support the general hypothesis that CSD could activate the trigeminovascular system by leading to neurogenic inflammation that ultimately causes migraine headaches”). Accordingly, from the evidence submitted herein, **not all** subjects treated for headaches have **CSD** (as recited in Claim 1). So even if Harris ‘828 discloses treating headaches, Harris ‘828 does not inherently disclose treating or preventing conditions associated with CSD, or even headaches associated with CSD.

The Office Action bridging p. 6-7 states

[w]ith respect to the term “prevention” please note that it does not require that the subject be afflicted with the disease. Thus, administration to a subject (e.g., Examples 1-7, pages 15-18) reads upon prevention of a condition associated with cortical spreading depression (CSD) in a subject including the conditions of instant claims 41 and 46.

Applicant is uncertain of the conclusion drawn by this statement. However, if it is intended to mean that a method of “preventing” a condition associated with CSD is expressly or inherently found in Harris ‘828, this is incorrect. As set forth above, CSD is not expressly mentioned in Harris ‘828. Treating migraine headaches does not inherently include treating conditions associated with CSD, including migraine headaches with CSD. Accordingly, there is no disclosure of treating, much less preventing, a condition associated with CSD in Harris ‘828.

Furthermore, the Office Action fails to address the element of Claim 1: administering to the subject harkoseride **in an amount effective to suppress CSD**. Again, Harris ‘828 fails to expressly disclose CSD and thus, does not disclose administering harkoseride in an amount effective to suppress CSD, or provide teaching/examples of what that amount would be. Harris ‘828 also fails to inherently disclose administration in an amount effective to suppress CSD because not **all** migraine headaches are associated with CSD. Mere disclosure of migraines is not sufficient to anticipate Applicant’s administration of harkoseride in an amount effective to suppress CSD.

Therefore, Claim 1 is novel over Harris ‘828.

1.2. Harris ‘828 Fails to Expressly and Inherently Disclose CSD: Claim 44 Is Novel

Claim 44 recites a method of suppressing CSD thereby preventing a migraine. Although a distinct independent claim, Claim 44, for at least the same reasons as stated above, is novel. Since Harris ‘828 fails to disclose CSD, there is no express anticipation; and, since all migraine headaches do not include CSD, merely treating migraines does not necessarily include suppression of CSD, much less suppression of CSD to prevent the migraine. Accordingly, mere disclosure of treating migraines does not expressly or inherently anticipate Claim 44.

1.3. Harris ‘828 Fails to Expressly and Inherently Disclose Specifically Claimed Headaches: Claim 46 Is Novel

Claim 46 recites a method for preventing or treating a headache selected from the group consisting of a muscle contraction headache, a toxic headache, a cluster headache, a traction headache, or an inflammatory headache. The Office Action fails to articulate any reason why Claim 46 is anticipated by Harris ‘828. Since Harris ‘828 fails to expressly or

inherently disclose treatment or prevention of any of the *Markush* group of headaches, Claim 46 is novel over Harris '828.

1.4. 35 U.S.C. §102(b) Over Harris '828 : Conclusion

Claims 2-4, 14, 16-18, 20, 24, 32-36, 41, 47 each depend directly or indirectly from Claim 1 or Claim 46, and are, thus, novel for at least the same reasons that Claim 1 and Claim 46 are novel. Withdrawal of the present rejection under 35 U.S.C. §102(b) is respectfully requested.

2. Rejection Under 35 U.S.C. §102(e)

Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, and 46-47 stand rejected under 35 U.S.C. §102(e) over US Patent 6,884,910 (herein "the Harris '910 patent). This rejection is respectfully traversed.

Because Harris '828 and the Harris '910 patent contain parallel disclosure, all arguments presented above for the rejection involving Harris '828 also apply to the present rejection. For at least the same reasons as stated above, Claims 1-4, 14, 16-18, 20, 24, 32-36, 41, 44, and 46-47 are novel over Harris '910.

Withdrawal of the present rejection under 35 U.S.C. §102(e) over Harris '910 is respectfully requested.

3. Rejection Under 35 U.S.C. §103(a) Over Harris '828 and Harris '910

Claims 1, 26-31, 42-45, and 52 stand rejected under 35 U.S.C. §103(a) over US Patent Application 2002/0086828 Harris (herein "Harris '828") and over US Patent 6,884,910 (herein "Harris '910"). This rejection is respectfully traversed.

For ease of review and because Harris '828 and the Harris '910 patent contain parallel disclosure, all arguments presented below refer and cite to Harris '828.

A. Claim 1

a. Harris '828 and Harris '910 Do Not Teach or Suggest a Method To Treat or Prevent A Condition Associated With CSD

All claim limitations must be considered in judging the patentability of a claim against the prior art. *See* MPEP 2143.03, *citing In re Wilson*, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970). If a reference is missing claimed features, there must be some apparent reason either in the reference or the general knowledge in the art to modify the reference to include the

missing subject matter. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ 1385 (2007). As stated above, Claim 1 is directed to a method to treat or prevent a condition associated with CSD, including by administering a CSD suppressive amount of harkoseride. The cited documents fail to disclose at least the following claim elements:

- (1) CSD, and
- (2) an amount of harkoseride effective to suppress CSD.

Harris '828 deals with "treating pain, in particular neuropathic pain, bipolar disease and migraine headaches." *See* Harris '828, at abstract. While Harris '828 does report a method of treating pain associated, in part, with migraine headaches, Applicant's invention is directed to a method of treating or preventing conditions associated with CSD. As shown above, CSD does not occur in all migraines, and CSD is associated with a number of other conditions not remotely related to migraines. Harris '828 fails to provide disclosure, teaching or suggestion of (1) treating migraine headaches associated with CSD, (2) treating other conditions associated with CSD such as cerebrovascular diseases, intracranial hemorrhage, head injury or transient global amnesia, and (3) an effective amount of harkoseride to suppress CSD. How could Harris '828 provide guidance to an ordinary artisan regarding an amount effective to prevent or treat a condition associated with CSD, when Harris '828 does not mention CSD?

Further, the Examiner fails to provide any rationale for an ordinary artisan to modify Harris '828 into a method of treating or preventing a condition associated with CSD, much less to modify Harris '828 to include administration of harkoseride in an amount effective to suppress CSD. Therefore, for at least this reason a presumption of *prima facie* obviousness has not been established for Claim 1 over Harris '828 or Harris '910.

b. A Method To Treat or Prevent A Condition Associated With CSD Is Unpredictable

Additionally, a method to treat or prevent a condition associated with CSD by administering an amount of harkoseride effective to suppress CSD is unpredictable. Applicant submits the following evidence of unpredictability.

"The underlying mechanism and physiological role of these blood flow related changes observed in CSD are still not fully understood." *See* application as filed, at p. 8, lines 9-11. Furthermore, Iadecola questions "what triggers CSD" and suggests that, at times, "the

mechanisms triggering CSD remain obscure.” Iadecola, at p. 111, col. 3; *see also* Ebersberger, at p. 11, col. 2 (“collectively, these results do not support the general hypothesis that CSD could activate the trigeminovascular system by leading to neurogenic inflammation that ultimately causes migraine headaches”). If the triggering mechanisms are obscure and CSD is not fully understood itself, how could the ordinary artisan predict that harkoseride would work to treat or prevent a condition associated with CSD, much less what would be the effective amount of harkoseride to suppress CSD. Rather, the evidence of a lack of understanding CSD, suggests that the “likely” outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. (Applicant stresses that the standard for nonobviousness is not expectation of failure, but lack of reasonable expectation of success. A showing of expectation of failure just makes the case for nonobviousness stronger.)

In this unpredictable, complex art, Applicant was the first to identify harokseride as a compound that could prevent or treat a condition associated with CSD by administering an amount of harkoseride which suppresses CSD. Accordingly, it could not have been predicted that harkoseride, although known to be effective in reducing pain in migraine headaches generally, could actually suppress CSD and thus treat or prevent conditions associated with CSD. Therefore, for at least this additional reason a presumption of *prima facie* obviousness has not been established for Claim 1 over Harris ‘828 or Harris ‘910.

B. Claim 44 and Claim 52

a. Harris ‘828 and Harris ‘910 Do Not Teach or Suggest a Method To Suppress CSD

Independent Claims 44 and 52 are directed to a method of suppressing CSD, by administering harkoseride. As set forth above, the cited documents fail to disclose the element CSD, much less teach or suggest a method for suppressing CSD. Harris ‘828 deals with “treating pain, in particular neuropathic pain, bipolar disease and migraine headaches.” *See* Harris ‘828, at abstract. While Harris ‘828 is directed to pain associated, in part, with migraine headaches, Applicant’s invention is directed a method to suppress CSD. As discussed above, not all migraine headaches are associated with CSD and Harris makes no disclosure, teaching, or suggestion of CSD-related migraine treatment. *See* MPEP 2143.03,

citing *In re Wilson*, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970) (all claim limitations must be considered in judging the patentability of a claim against the prior art); *see also KSR, supra*. Further, without any mention of CSD, there is no rationale for modifying Harris '828 into a method of suppressing CSD. Therefore, for at least this reason a presumption of *prima facie* obviousness has not been established for Claim 44 or Claim 52 over Harris '828 or Harris '910.

b. A Method To Suppress CSD Is Unpredictable

Additionally, a method to suppress CSD is also unpredictable for at least the same reasons as presented in Sec. 3(A) for Claim 1. Therefore, also for at least this reason a presumption of *prima facie* obviousness has not been established for Claim 44 or Claim 52 over Harris '828 or Harris '910.

C. Dependent Claims

Claims 26-31 and 42-43 each depend directly or indirectly from Claim 1 and are, thus, non-obvious at least for all of the aforementioned reasons that make Claim 1 non-obvious.

Claim 45 depends from Claim 44, and is thus non-obvious at least for all of the aforementioned reasons that make Claim 44 non-obvious.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

4. Rejection Under 35 U.S.C. §103(a) Over Harris '828 and Harris '910

Claims 40 and 44-48 stand rejected under 35 U.S.C. §103(a) over US Patent Application 2002/0086828 Harris (herein "Harris '828") and over US Patent 6,884,910 (herein "Harris '910"). This rejection is respectfully traversed

A. Claim 40

The Office Action contains no discussion of why Claim 40 is *prima facie* obvious in view of Harris '848 or Harris '910. Claim 40 ultimately depends from Claim 1. Therefore a presumption of *prima facie* obviousness has not been established for Claim 40 over Harris '848 or Harris '910 for at least the same reasons as Claim 1 (*see* Sec. 3(A)).

B. Claim 44

The Office Action contains no discussion of why Claim 44 is *prima facie* obvious in view of Harris '848 or Harris '910. Independent Claim 44 is directed to a method of

suppressing CSD thereby preventing a migraine in a subject, the method comprising orally administering to the subject harkoseride. Applicant references Sec. 3(B) above which more fully articulates the reasons why a presumption of *prima facie* obviousness has not been established for Claim 44 over Harris '848 or Harris '910.

C. Claim 46

The Office Action provides no discussion of why Claim 46 is *prima facie* obvious in view of Harris '848 or Harris '910. Independent Claim 46 is directed to a method of preventing or treating a headache selected from the recited Markush group by administering an oral effective amount of harkoseride. Although Harris '828 and Harris '910 report on treatment for headaches such as migraines, Harris '828 and Harris '910 do not teach or suggest any of the types of headaches recited in Claim 46's Markush group. Therefore, a presumption of *prima facie* obviousness has not been established for Claim 46 over Harris '848 or Harris '910.

D. Dependent Claims 45, 47-48

In making this second 103 rejection, the Examiner's discussion is limited to administering an agent, such as a triptan, in addition to harkoseride, and the recited dosages in the dependent claims. None of the Examiner's discussion addresses the fact that neither Harris '828 nor Harris '910 teaches or suggests (1) a method for suppressing CSD (Claim 44) nor (2) a method for preventing or treating any of the headaches recited in Claim 46. Therefore, a presumption of *prima facie* obviousness over Harris '828 or Harris '910 has not been established.

5. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Office Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,
HARNESS, DICKEY & PIERCE, P.L.C.

/ Leanne M. Rakers /

Leanne M. Rakers
Attorney for Applicant
Reg. No. 64,412
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, Missouri 63105
314.726.7514 (direct)
314.726.7501 (fax)